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Development of tissue-selective gene delivery system with ultrasound

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Gene therapy is applied into cardiovascular diseases, cancer and diseases that are due to genomic causes. Viral vectors are efficient carriers of genes for transduction, but some problems have become evident. Delivery vectors that are highly potent in terms of gene transduction efficiency should also be safe and easy to apply. Non-viral vectors have recently received focus as gene carriers, but their transduction efficiency is very low and not suitable for *in vivo* gene delivery. In addition, it is important to develop tissue-specific or selective gene delivery system to avoid side effects in gene therapy. However, the gene delivery system which can easily change a transfection site has not been developed. Gene delivery with ultrasound is expected to be an attractive method for controlling gene delivery site due to induced driving force of gene transfection at the limited area where it is insonated. In this study, we assessed the feasibility of tissue selective gene delivery with nanobubbles and ultrasound exposure.

Gene delivery into liver or brain – Luciferase coded plasmid DNA (pCMV-Luc) (100 μg) and nanobubbles (500 μg) suspension was injected into the tail vein of mice. Then, US was transdermally exposed to liver (frequency: 1 MHz, 1 W/cm^2, 1 min) or transcranially exposed to brain (frequency: 1 MHz, 1.2 W/cm^2, 1 min). After 1 day of injection, the luciferase expressions were measured. When ultrasound was exposed to liver, luciferase expression in the liver was higher than that in other tissues (Fig. 1). On the other hand, when ultrasound was exposed to brain, luciferase expression was observed in the brain. From these results, it was suggested that the tissue of gene delivery was controllable by changing the site of ultrasound exposure.

In addition, we confirmed the gene expression cells in gene delivery for liver. In this case, gene expression was observed in parenchymal cells. Moreover, we also confirmed the parts of gene expression in the brain after gene delivery. Gene expression was observed at wide area in the brain. From these results, it is guessed that plasmid DNA might be extravasated with jet stream induced by cavitation of nanobubbles and delivered into parenchymal cells in the liver and brain. Therefore, the combination of nanobubbles and ultrasound exposure would be a non-invasive and tissue selective gene delivery system.

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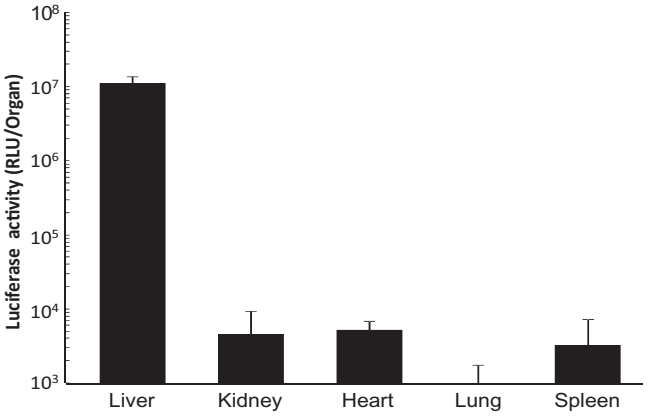

Fig. 1 – Luciferase expression with nanobubble and ultrasound exposure for liver.

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